

WHAT IS CLAIMED IS:

1. A cellular expression system capable of exchanging at least one target gene, comprising:

- a. a first integration cassette which comprises
 - i. a first promoter operably linked to
 - ii. a first exchangeable reporter segment having a first scorable homeostatic reporter element, which comprises at least one scorable reporter gene and an exchangeable reporter gene, the first scorable homeostatic reporter element linked at its 5' end to a first recombinase recognition site, and at its 3' end to a second recombinase recognition site;

wherein the first integration cassette is capable of stable and random insertion into one or more first discrete genomic positions in a host cell, thereby creating a recombinant cell population;

- b. a first target cassette comprising a first exchangeable target segment having:
 - i. a third recombinase recognition site, capable of recognizing the first recombinase recognition site in the first integration cassette,
 - ii. a first target element;
 - iii. a fourth recombinase recognition site, capable of recognizing the second recombinase recognition site in the first integration cassette;

wherein the first target element is linked at its 5' end to the third recombinase recognition site, and at its 3' end to the fourth recombinase recognition site; and

- c. at least one rec element encoding at least one recombinase activity recognizing the recombinase recognition sites of a and b,

wherein introduction of the rec element and the first target cassette to the recombinant cell population results in site-specific substitution of the first exchangeable reporter segment with the first exchangeable target segment at the first discrete genomic position.

2. The cellular expression system of Claim 1, wherein the rec element is included in the first integration cassette.

3. The cellular expression system of Claim 1, wherein the rec element is included in the first target cassette.
4. The cellular expression system of Claim 1, wherein the recombinase activity is selected from the group consisting of Flp recombinase, Cre recombinase, Int recombinase, Sin recombinase and Hin recombinase.
5. The cellular expression system of Claim 1, wherein the host cell is selected from the group consisting of mammalian cells, yeast cells and bacterial cells.
6. The cellular expression system of Claim 1, wherein the first integration cassette further comprises a polycistronic element.
7. The cellular expression system of Claim 1, wherein the first integration cassette further comprises a TAG sequence.
8. The cellular expression of Claim 1, wherein the first target element further comprises a first target gene and a first selectable marker gene.
9. The cellular expression system of Claim 8, wherein the first target cassette further comprises a polycistronic element.
10. The cellular expression system of Claim 1, wherein the first target cassette further comprises a TAG sequence.
11. The cellular expression system of Claim 1 further comprising:
 - d. a second integration cassette which comprises
 - i. a second promoter operably linked to
 - ii. a second exchangeable reporter segment having a second scorable homeostatic reporter element, which comprises at least one scorable reporter gene and an exchangeable reporter gene, the second scorable homeostatic reporter element linked at its 5' end to a fifth recombinase recognition site, and at its 3' end to a sixth recombinase recognition site;

wherein the second integration cassette is capable of stable and random insertion into one or more second discrete genomic positions in a mammalian cell; and

e. a second target cassette comprising a second exchangeable target segment having:

- i. a seventh recombinase recognition site, capable of recognizing the fifth recombinase recognition site in the second integration cassette;
- ii. a second target element;
- iii. an eighth recombinase recognition site, capable of recognizing the sixth recombinase recognition site in the second integration cassette;

wherein the second target element is linked at its 5' end to the seventh recombinase recognition site, and at its 3' end to the eighth recombinase recognition site; and

f. a recombinase activity capable of recognizing the recombinase recognition sites of d and e;

wherein introduction of the second target cassette to the recombinant cell population results in site-specific substitution of the second exchangeable reporter segment with the second exchangeable target segment at the second discrete genomic position.

12. The cellular expression system of Claim 11, wherein the second integration cassette further comprises a TAG sequence.

13. The cellular expression system of Claim 11, wherein the second integration cassette further comprises a polycistronic element.

14. The cellular expression system of Claim 11, wherein the second target element further comprises a second target gene and a selectable marker.

15. The cellular expression system of Claim 14, wherein the second target cassette further comprises a polycistronic element.

16. The cellular expression system of Claim 11, wherein the second target cassette further comprises a TAG sequence.
17. The cellular expression system of Claim 11, wherein the first and second target elements each encode one subunit of a protein complex.
18. The cellular expression system of Claim 17, wherein the protein complex is an antibody.
19. The cellular expression system of Claim 11, wherein the first and second target elements encode one or more cloning sites.
20. An antibody library comprising:
 - a cell population, each cell of the cell population having a first integration cassette and a second integration cassette stably integrated at discrete genomic positions;
 - the first integration cassette comprising a promoter operably linked to a first nucleic acid encoding a first peptide for an antibody, the first nucleic acid linked at its 5' end to a first recombinase recognition site, and at its 3' end to a second recombinase recognition site; and
 - the second integration cassette comprising a promoter operably linked to a second nucleic acid encoding a second peptide for an antibody, the second nucleic acid linked at its 5' end to a third recombinase recognition site and at its 3' end to a fourth recombinase recognition site;
 - whereby the first and second nucleic acids are expressed at equal levels in each cell of the cell population.
21. The antibody library of Claim 20, wherein the first nucleic acid comprises variable sequences.
22. The antibody library of Claim 20, wherein the second nucleic acid comprises variable sequences.
23. The antibody library of Claim 20, wherein the first peptide is an antibody light chain peptide and the second peptide is an antibody heavy chain peptide.

24. The antibody library of Claim 20, wherein the first and second peptides are Fab peptides.
25. The antibody library of Claim 20, wherein the first and second peptides are Fab' peptides.
26. The antibody library of Claim 20, wherein the first and second nucleic acids encode a humanized antibody peptide.
27. An integration cassette comprising:
- a. a promoter operably linked to
 - b. an exchangeable reporter segment having a scorable homeostatic reporter element, which comprises at least one scorable reporter gene and an exchangeable reporter gene, the first scorable homeostatic reporter element linked at its 5' end to a first recombinase recognition site, and at its 3' end to a second recombinase recognition site;
- wherein the integration cassette is capable of stable and random insertion into one or more discrete genomic positions in a host cell.
28. The integration cassette of Claim 27 further comprising a TAG sequence.
29. The integration cassette of Claim 27 further comprising a polycistronic element.
30. A method for selecting a transformed cell population capable of exchanging nucleic acid segments, comprising:
- a. obtaining a first integration cassette as in Claim 1(a) ;
 - b. introducing the first integration cassette into cells, creating a recombinant cell population with the first integration cassette stably inserted at one or more first discrete genomic positions within each cell;
 - c. scoring the level of expression of the first scorable homeostatic reporter element; and

- d. selecting from the recombinant cell population those cells scoring a first predetermined level of expression for the first scorable homeostatic reporter element.
31. The method of Claim 30, further comprising:
- e. introducing to the selected recombinant cell population
 - i. a first target cassette as in Claim 1(b);
 - ii. a rec element encoding recombinase activity recognizing the recombinase recognition sites of the first integration cassette and the first target cassette;
- whereby the first exchangeable target segment is substituted for the first exchangeable reporter segment at the first discrete genomic positions.
32. The method of Claim 31, wherein the recombinase activity of step (e) is chosen from the group consisting of F1p recombinase, Cre recombinase, Int recombinase, Sin recombinase and Hin recombinase.
33. The method of Claim 30, wherein the first discrete genomic positions of step (b) are chromosomal.
34. The method of Claim 30, wherein the first discrete genomic positions of step (b) are extrachromosomal.
35. The method of Claim 30, wherein the scorable reporter gene encodes a surface antigen.
36. The method of Claim 31, wherein the first target element further comprises a first target gene and a first selectable marker gene.
37. The method of Claim 36, wherein substitution of the first exchangeable target segment for the first exchangeable reporter segment is monitored by screening for the absence of the scorable reporter gene and the presence of the first selectable marker gene.

38. The method of Claim 30, wherein step d further comprises isolating a single cell from the population of cells scoring a first predetermined level of expression for the first scorable homeostatic reporter element, and

the method further comprising:

e. expanding the single cell to form a clonal cell population, wherein the first integration cassette is stably inserted at the same first discrete genomic positions within each cell of the clonal cell population.

39. The method of Claim 31, wherein the first target element of step (e) has a secretory signal element.

40. The method of Claim 31, further comprising:

f. obtaining a second integration cassette as in Claim 11(d);

g. introducing the second integration cassette into the recombinant cell population of Claim 30, thereby creating a second recombinant cell population with the second integration cassette inserted randomly at one or more second discrete genomic positions within each cell of the second recombinant cell population;

h. scoring the level of expression of the second scorable homeostatic reporter element for each cell of the second recombinant cell population; and

i. selecting from the second recombinant cell population those cells scoring a second predetermined level of expression for the second scorable homeostatic reporter element;

wherein the selected cells comprise the second integration cassette stably integrated at one or more second discrete genomic positions and the first integration cassette stably inserted at one or more first discrete genomic positions within each cell.

41. The method of Claim 40, wherein the first scorable homeostatic reporter element and the second scorable homeostatic reporter element are expressed at equivalent levels.

42. The method of Claim 40, wherein the first scorable homeostatic reporter element and the second scorable homeostatic reporter element are expressed at a preselected ratio.

43. The method of Claim 40, wherein the second integration cassette further comprises a polycistronic element.
44. The method of Claim 40, wherein the second integration cassette further comprises a TAG sequence.
45. The method of Claim 40, wherein the second scorable homeostatic reporter element comprises a scorable reporter gene and an exchangeable reporter gene that differs from the first scorable homeostatic reporter element.
46. The method of Claim 40, further comprising:
introducing to the second recombinant cell population;
- i. a first target cassette as in Claim 1(b);
 - ii. a second target cassette as in Claim 11(e);
 - iii. a rec element encoding recombinase activity recognizing the recombinase recognition sites of the first and second integration cassettes and first and second target cassettes;
- wherein the first exchangeable target segment is substituted for the first exchangeable reporter segment at the first discrete genomic positions, and the second exchangeable target segment is substituted for the second exchangeable reporter segment at the second discrete genomic positions.
47. The method of Claim 46, wherein the first target cassette and the second target cassette encode subunits of a multi-subunit complex.
48. The method of Claim 47, wherein the multi-subunit complex is an enzyme.
49. The method of Claim 47, wherein the multi-subunit complex is an antibody.
50. A site-specific expression system comprising a recombinant cell population having an integration cassette as in Claim 1(a), wherein the integration cassette is stably and randomly inserted at one or more discrete genomic positions within each cell of the recombinant cell population and wherein the homeostatic reporter element and the target element is expressed.

51. An antibody producing recombinant cell population, each cell of the recombinant cell population having a first integration cassette as in Claim 1(a) and a second integration cassette as in Claim 11(e), wherein each integration cassette is stably and randomly inserted at a first and second discrete genomic position, respectively, in each cell of the recombinant cell population, and wherein the first and second integration cassette is substituted with a first exchangeable target segment as in Claim 1(b) and a second exchangeable target segment as in Claim 11(f), wherein the first and second exchangeable target segment encodes an antibody chain, whereby the antibody chains encoded by the first and second exchangeable target segment is expressed at equivalent levels in each cell of the recombinant cell population.

52. The antibody producing recombinant cell population of Claim 51, wherein the recombinant cell population is clonal in origin.

53. The antibody producing recombinant cell population of Claim 51, wherein the antibody chains comprise a light chain and a heavy chain.

54. The antibody producing recombinant cell population of Claim 53, wherein the heavy chain corresponds to a heavy chain Fab fragment.

55. The antibody producing recombinant cell population of Claim 53, wherein the heavy chain corresponds to a heavy chain Fab' fragment.

56. A recombinant expression cell line comprising:
a recombinant cell line having an integration cassette as in Claim 1(a), wherein the integration cassette is stably inserted at a discrete genomic position that is identical in each cell of the recombinant cell line.

57. The recombinant expression cell line of Claim 56, wherein the integration cassette further comprises a polycistronic element.

58. The recombinant expression cell line of Claim 56, wherein the integration cassette further comprises a TAG sequence.

59. A method of making an antibody library comprising:
- a. obtaining a second recombinant cell population as in Claim 40(g); wherein the first scorable homeostatic reporter element and the second scorable homeostatic reporter element are expressed at equivalent levels in the second recombinant cell population;
 - b. introducing a first target cassette having a first target element as in Claim 1(b), wherein the first target element encodes a first peptide for an antibody; and
 - c. introducing a second target cassette having a second target element as in Claim 11(e), wherein the second target element encodes a second peptide for an antibody;
- whereby the first and second target elements are expressed at equal levels in each cell of the cell population.
60. The method of Claim 59, wherein the first peptide comprises variable sequences.
61. The method of Claim 59, wherein the second peptide comprises variable sequences.
62. The method of Claim 59, wherein the first peptide is an antibody light chain peptide and the second peptide is an antibody heavy chain peptide.
63. The method of Claim 59, wherein the first and second peptides are Fab peptides.
64. The method of Claim 59, wherein the first and second peptides are Fab' peptides.
65. The method of Claim 59, wherein the first and second peptides are humanized antibody peptides.